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Amebiasis, Today, in the United States

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● *A most important factor in the detection of amebiasis is to entertain the diagnosis* first. *Appropriate search for the parasite should precede other diagnostic or therapeutic efforts which may mask the correct diagnosis for weeks. An alert suspicious physician with competence at the microscope can save the patient from amebic neurosis secondary to over diagnosis as well as chronic ill health and possible death related to underdiagnosis.*

ALTHOUGH MAN FIRST SAW the organism Entamoeba hystolytica in 1875 and recognized its relationship to disease some ten years later, D'Antoni could say as recently as 1949 that "the majority of physicians know little about amebiasis and what knowledge they have is usually incorrect."[1] In view of increasing civilian and military travel as well as continuing endemicity of amebiasis in North America, it seems worthwhile to reemphasize this important infection as seen in the United States.

The diagnosis of amebiasis is subject to three major problems. One of them is clinical underdiagnosis. Amebiasis is often not considered unless the patient has recently returned from the tropics, but the interval between travel exposure and the development of overt disease may be over 30 years. While it is true that travel to developing countries enhances the likelihood of symptomatic disease, it is not necessary to have an exotic travel history to have amebiasis; by conservative estimate 5 percent of the untraveled U.S. population harbors E. histolytica.[2] A second problem, related to the poor correlation between the prevalence of amebas and amebic disease, results in over-diagnosis of clinical amebiasis in response to a laboratory report of E. histolytica. It is well to bear in mind that at least 90 percent of persons who have E. histolytica in stools are asymptomatic cyst carriers whose present illness (if any) is totally unrelated to this finding. Unfortunately, as Elsdon-Dew has noted, amebas have been blamed for nearly every condition except pregnancy.[3] The third problem is missed laboratory diagnosis. Although laboratory proficiency is generally at a low level, many physicians rely entirely on the findings of their clinical laboratories to confirm or deny a diagnosis of amebiasis.[2] The difficulty in identifying E. histolytica, particularly from a symptomatic patient, has been over-emphasized, and every physician should attempt to identify this parasite himself. Prompt examination of a fresh stool specimen by a novice is frequently as informative as examination of an old stool, as received in the laboratory (where, by the way, it is often seen by an equally unexperienced technician).

Etiology

Man becomes infected by ingestion of food or water contaminated with fecal material containing cysts of E. histolytica. Swallowed viable cysts liberate trophozoites in the intestine near the

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cecum. The motile vegetative trophozoite is the only form of E. histolytica which is parasitic in man. It is the bowel transit time which determines whether cysts or trophozoites are found in the stool: During normal slow passage through the colon, trophozoites encyst; with purgatives or diarrhea some trophozoites, carried rapidly to the outside, can be found in liquid stool.

It is unknown why the majority of infections, particularly those acquired in the United States, are asymptomatic. A good diet is believed to enhance commensalism and reduce pathogenicity of amebic infection. Travel, fatigue, stress, surgical operation or pregnancy precipitate symptoms in some patients. E. hartmani, formerly called small race E. histolytica (cysts less than 10μ in size), apparently never invades tissue and may account for many asymptomatic infections.[4,5]

Clinical Diagnosis of Intestinal Amebiasis

Patients with amebiasis may present with acute febrile dysentery suggestive of shigellosis, with chronic dysentery or diarrhea suggestive of ulcerative colitis or regional enteritis, or with intermittent diarrhea or constipation suggestive of carcinoma of the colon. The illness may be of three hours' or 30 years' duration. Cases of long standing are frequently misdiagnosed as irritable colon or psychoneurosis. A complete review of amebic symptomatology is given in Wilmont's book.[6] Since symptoms are usually too non-specific to suggest the diagnosis, when evaluating a patient with complaints referable to the lower gastrointestinal tract, amebiasis must be considered first, before barium studies, mineral oil preparations, tap water enemas, or antibiotics obscure the diagnosis.

While typically the patient with uncomplicated intestinal amebiasis has no fever, anemia or leukocytosis, these systemic manifestations are seen with fulminating intestinal amebiasis. Death may result from failure to appreciate that amebiasis can cause severe illness. Corticosteroid therapy exacerbates intestinal amebiasis and surgical treatment of unrecognized amebiasis also carries a serious risk to life.

Laboratory Diagnosis

Microscopic examination of the stool is the only sure way to establish the diagnosis of intestinal amebiasis. While the absence of pus cells or the presence of Charcot-Leyden crystals is suggestive, the identification of the parasite is necessary to confirm the diagnosis. In more than 90 percent of patients with symptoms due to intestinal amebiasis the organism will be found in fecal specimens if they are examined correctly—repeatedly if necessary—before other diagnostic or therapeutic measures are taken.[7,8] (Table 1). Specimens obtained by proctoscopic examination or in the course of rectal biopsy are rarely diagnostic in the face of negative stool examinations, except for patients in whom diagnostic efforts or antibiotics have obscured the presence of the ameba. If material is to be obtained at direct examination, solid objects such as spatulas or pipettes should be used rather than cotton swabs, for ameba may cling to swabs and not be transferred to the slide. Patients with diarrhea need no preparation for sigmoidoscopy; for those who do not have diarrhea preparation should be done with a normal saline solution enema (not tap water or soapsuds).

All stool specimens should be examined fresh. Warming will not restore motility, and may dry out and destroy trophozoites. A pin-head size piece of stool is sufficient. The preparation should be thin enough to read newsprint through. With most specimens this requires dilution with saline solution, which should be placed on the slide before the stool is added. (Water should not be used, as it will alter trophozoites.) Examination of unstained specimens should start under low power, with higher magnification used for delineation of suspicious findings.

The distinguishing features of E. histolytica

TABLE 1.—*Diagnosis of Intestinal Amebiasis*

Method	*Diagnostic efficacy (Percent)*
Microscopic examination of stool:	
without diarrhea—3 formed and 1 purged stool*	90
with diarrhea—6 stools	> 95
Sigmoidoscopy—pustules, ulcers or nodules	< 50
Barium enema—some abnormality	25
Serologic diagnosis—IHA or agar gel	85

*Two ounces of satured solution of sodium sulfate is the best purgative and will result in a diarrheal stool within 4 hours (usually less). The diagnostic efficacy of stool examination assumes that the patient has not received barium or mineral oil preparations within the preceding 2 weeks; and has not received antibiotics within the past month; these procedures will often eradicate identifiable amebas without curing the patient.

TABLE 2.—*Identification of E. histolytica (large race)*

	Unstained	*KI (D'Antoni's)*	*Iron-hematoxylin*
Trophozoite	Progressive motility		Delicate nucleus with central karyosome
	Clear pseudopod		
	Invisible nucleus		
	Ingested RBC		
Cyst	Small pearls, identifiable as E. histolytica only when chromatoid bars with rounded ends (sausages) are seen	1-4 ring-like nuclei 2 times RBC size	Delicate nuclei with central karyosome Rounded chromatoidals

Note: Unstained smears are best for identification of trophozoites; iron hematoxylin may be required for identification of cysts or of trophozoites which have lost their motility. Not all findings are necessarily present; *i.e.* E. histolytica trophozoites may have no ingested erythrocytes; cysts, no visible chromatoidals.

In contrast, the trophozoites of Entameba coli have sluggish non-progressive motility, granular cytoplasmic pseudopods, and a usually visible nucleus in the unstained preparation. Cysts of E. coli are approximately twice the size of E. histolytica. They contain up to 8 nuclei which are visible in unstained preparations and show a coarse nuclear pattern with a larger excentric karyosome in stained preparations. Chromatoidals, when present, have ragged ends.

are noted in Table 2. While "rip-snorting, galloping, blood-thirsty" trophozoites[3] are characteristic of amebic dysentery, in patients who do not have dysentery the parasites are often somewhat less active and contain debris rather than erythrocytes. Such forms may require stained preparations for differentiation from Entameba coli, other amebas, macrophages and the like. To avoid overdiagnosis: When in doubt, throw it out—E. histolytica looks remarkably like E. histolytica!

Unpurged specimens in chronic or asymptomatic cases may contain only cysts. In unstained preparations cysts resemble small pearls which cannot be separated from those of E. coli unless chromatoid bars with rounded ends are visible. Cysts are better identified in fresh specimens by staining with D'Antoni's solution, which demonstrates the number of nuclei, or by iron-hematoxylin staining which demonstrates nuclear structure. Chromatoidals are also visible with the latter stain, and it also permits preservation of slides for mailing when diagnostic confirmation is necessary. Stool can also be preserved in polyvinyl alcohol (PVA) fixative for examination at a later date.

The number of cysts in the stool varies from day to day; intervals of several weeks may pass between positive stools.[9] Concentration techniques, such as the zinc sulfate method, increase the diagnostic yield in such cases.[10]

As noted in Table 1, other diagnostic methods are inferior to appropriate stool examination. Abnormalities on sigmoidoscopic examination are seen in less than half of cases, reflecting the greater frequency of cecal than rectosigmoid infection.[11] Occasionally sigmoidoscopic findings are sufficiently characteristic to suggest a diagnosis of amebiasis even without previous suspicion.[12] Ulcers, usually covered with a white cap, lying on normal intervening mucosa are suggestive. If the ulcers are elongated (like a knife-cut), or if scraping leaves a bleeding base much larger than the ulcer appeared superficially (collar-button ulcer), a presumptive diagnosis of amebiasis can be made. Confirmation by finding typical trophozoites is not difficult in such cases and should always be attempted.

Barium enema study is likewise a low-yielding diagnostic method for amebiasis, with abnormalities observed in less than 25 percent of cases.[12] Individual ulcers are usually too shallow to be seen roentgenographically, although multiple ulcerations may result in minimal irregularity or granularity of the mucosal pattern best seen on post-evacuation films. Granularity, lack of distensibility and narrowing of the lumen, which are the most common radiographic findings,[13] are not specific for amebiasis. A less common but more helpful finding is concentric inflammatory involvement of the cecum, often with a skip area of disease in another segment of the bowel, especially the rectosigmoid area; if skip lesions are present and the terminal ileum is normal,

ulcerative colitis or regional enteritis is unlikely. An ameboma usually appears as symmetrical concentric narrowing of the cecum without rigidity, features which make it readily distinguishable from the asymmetrical irregular defect seen with carcinoma of the cecum.

Serologic techniques are now available for the diagnosis of amebiasis. Indirect hemagglutination tests and agar gel diffusion give positive results when significant tissue invasion has occurred, but are usually negative for asymptomatic patients.[14] Thus a positive result is most likely to be obtained from the patient with typical trophozoites in the stool. Unless one of these methods is available locally, the loss of time involved in awaiting results is a serious objection to serologic methods for the primary diagnosis of intestinal amebiasis. They are, however, occasionally useful for retrospective confirmation when use of mineral oil, barium or antibiotics has obscured the value of stool examination.

Diagnosis of Liver Abscess

Amebic liver abscess occurs in less than 1 percent of patients with intestinal infections, but recognition and treatment of it may be a medical emergency. Fever is the most frequent manifestation that brings the patient to the doctor.[15] A typical patient also has an enlarged tender liver, anemia and leukocytosis, but one or more of these findings are absent in up to 15 percent of cases.[15,16] Less than half of patients with amebic liver abscess have a recent or remote history suggestive of intestinal amebiasis.

Table 3 summarizes the diagnostic approaches to amebic liver abscess. Hepatomegaly is the most frequent sign, provided careful attention is paid to upward as well as downward enlargement and chest roentgenograms are used to supplement physical examination. Elevation of the diaphragm—classically, anterior medial bulging —or immobility of the diaphragm is observed in more than 80 percent of patients.[16] Blunting of the costophrenic or cardiophrenic angle or platelike atelectasis of the right lower lobe are helpful features when present. A crescent shadow superimposed on the denser shadow of the hepatic cupola is also suggestive. Later, sympathetic or communicating pleural effusions or pneumonia may be seen. One or more abscesses, usually in the right lobe of the liver, can be localized by radioactive liver scan in the majority of cases.[17]

TABLE 3.—*Laboratory Diagnosis of Amebic Liver Abscess*

	Percent of Cases
Liver function tests (alkaline phosphatase, BSP) elevated in	< 25
Stools for *E. histolytica* positive in	< 50
Chest x-ray—elevated diaphragm, blunted costophrenic angle, atelectasis, effusion or pneumonia	80
Chest fluoroscopy—altered diaphragmatic motility	85
Liver scan (AP and lateral)—filling defect	95
Serologic tests (IHA or agar gel diffusion)	95
Aspiration of abscess—sterile pus of any character	85
Identification of amebas (serial tubes)	90
Liver biopsy of abscess wall	70

While drainage is not necessary in the majority of patients with amebic liver abscess, some will not respond to anti-amebic therapy until drainage has been carried out. Aspiration through a large-bore needle (required for withdrawal of thick pus) is usually associated with a dramatic decrease in both pain and fever. The hazards of closed aspiration of amebic liver abscess have been over-emphasized in the American literature. Aspiration of a liver abscess, especially one localized by scan or by point-tenderness or bulging on physical examination, provides the most secure differentiation between amebic and pyogenic liver abscesses. The aspirate may have any appearance, but chocolate or gelatinous red pus or sterile pus (less than 15 percent of amebic liver abscesses are secondarily infected) is very suggestive of an amebic liver abscess. When aspirate is divided into serial specimens as it is withdrawn, examination of the last specimen, representing the edge of the abscess, will demonstrate trophozoites in 90 percent of cases.[3] Biopsy of the edge of the abscess has also been successful for diagnostic confirmation.[18] To obtain the specimen, a Vim-Silverman needle (outer core only) is introduced until pus is aspirated and then withdrawn just to the point when pus can no longer be obtained. At that point the split inner needle is introduced and the biopsy specimen is taken in the usual way.

If aspiration is not attempted, the patient can be treated for both pyogenic and amebic liver

TABLE 4.—*Treatment of Amebiasis (adult dose based on 60 kg man)**

Condition	*Drug*	*Dose*	*Duration*
A. Mild or asymptomatic intestinal infection	diiodohydroxyquin	650 mg tid	20d
B. Symptomatic intestinal infection without fever or leukocytosis.	tetracycline	250 mg tid	5d *plus* A,D**
C. Severe intestinal disease (fever, leukocytosis, toxicity)	emetine hydrochloride	1 g qd	5d *plus* A,B,D**†
D. Liver abscess	emetine hydrochloride	1 g qd	10d *plus* A††
	and chloroquine phosphate	1 g qd ff by 500 mg qd	2d 20d

*The dosage varies by weight; emetine in particular must be given on a weight basis (1 mg per kg of body weight, not to exceed 65 mg). Emetine is given subcutaneously or intramuscularly; all other medications are given orally.

**Patients with no evidence of liver disease should receive chloroquine.

†Tetracycline should be given concomitantly with parenteral emetine for severe amebic dysentery. Diiodohydroxyquin and chloroquine are best given after the course of primary therapy for intestinal amebiasis is completed.

††Patients with no evidence of intestinal infection should receive diiodohydroxyquin.

abscess while awaiting results of serologic study of specimens mailed to a regional laboratory or the Center for Disease Control in Atlanta. The indirect hemagglutination test and agar gel diffusion method are positive in more than 95 percent of cases.[14]

It is well to remember that the two diagnostic methods most often used, although helpful when positive, are more frequently normal. Results of liver function tests (alkaline phosphatase and bromsulphalein) are within normal limits in approximately 75 percent of cases, and stools are positive for amebas in less than half.[15,16]

Treatment of Amebiasis

The chemotherapy of amebiasis has been unsatisfactory, as attested by the number of available drugs and the divergence of opinion in the literature about the drug of choice. The therapeutic quandary is compounded by the toxicity of the most active drugs, the usual need for at least two agents (a poorly absorbed drug effective in the tissue lumen against cysts and another drug for the trophozoite tissue phase) and the difficulty in differentiating relapse from reinfection in many endemic areas where drug trials have been conducted. No treatment is effective in all cases, and repeated stool examination for at least six months is necessary for confirmation of cure.

Controversy also clouds the merits of treating asymptomatic patients. Autopsy demonstration of bowel pathology in "healthy carriers" who died in accidents[19] and the sigmoidoscopic observation of abnormalities in up to 20 percent of asymptomatic cyst passers,[20] suggest that therapy should be carried out in all diagnosed cases in this country. Other valid arguments for the treatment of asymptomatic amebiasis include the potential for the infections of others and the possibility that the disease may become severe—and not properly attributed – following one of the poorly understood events which upset host-parasite balance.

Table 4 lists a reasonable treatment regimen meeting Food and Drug Administration approval. Patients with intestinal infection and no evidence of hepatic amebiasis should receive a course of chloroquine to circumvent the development of an unrecognized amebic liver abscess at a later date. Patients with liver disease should receive treatment for intestinal infection also, whether or not amebas are found in the stool. Fulminating intestinal amebiasis (characterized by dysentery, fever and leukocytosis) and amebic liver abscess are potentially fatal conditions and merit the most rapidly active drug, emetine, despite its well-known cardiovascular toxicity. Unfortunately, patients have died or have suffered needless complications because emetine was withheld on grounds of toxicity.

Combinations of drugs are usually required because some – diiodohydroxyquin by mouth, for example—have direct action only on parasites in the bowel lumen; some, such as the tetracyclines, have indirect action on the bowel lumen and bowel wall but no effect on amebas in the liver; some, such as parenteral emetine, are effective only in the tissues (bowel wall and liver); and some are effective only in the liver, chloroquine for example.

Metronidazole (Flagyl®) and niridazole (Ambilhar®) are the first drugs to be effective against

both intestinal and extraintestinal parasites. While the latter has been too toxic for general use, experience with Flagyl outside the United States suggests that it is safe, highly effective and currently the drug of choice for amebiasis.[4,5,21] The dose is 750 mg three times a day for five days for dysentery, 500 mg three times a day for five days for liver abscess. Unfortunately Flagyl has not yet received FDA approval for the treatment of amebiasis, and its use in most hospitals in the United States will therefore require approval of an experimental drug protocol.

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EARLY CHANGES OF GLAUCOMA

"A great variation exists in the size and configuration of normal physiologic optic disc cupping. This variation makes difficult the detection of earliest glaucomatous disc changes. If the examiner searches for widening of the cup as an early change, he is at a serious disadvantage if he does not have a clear record of the base-line size of a specific optic disc cup. If the examiner searches for the development of a furrow in a margin of the cup or for extensive shelving of the disc rim or for obvious signs of atrophy, such cases are often already associated with significant visual field loss. Yet since tonometry may at times be misleading and since precise examination of the visual fields is not widely practiced on a routine basis, the detection of early glaucomatous disc changes is highly desirable. Although the cupping of the individual disc may vary widely, cupping is almost always symmetrically similar in the two eyes of an individual. . . . Any asymmetry of disc cupping is an important alerting sign of possible glaucomatous change.

"For the ophthalmologist, the importance of recognizing asymmetrical cupping is in its indication of the need for further evaluation. For the non-ophthalmologist who routinely uses the ophthalmoscope but not the tonometer, disc asymmetry represents the most accessible early sign of glaucoma."

—RONALD S. FISHMAN, M.D., Washington, D.C.
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